CANCEROUS DISEASE MODIFYING ANTIBODIES

REFERENCE TO RELATED APPLICATIONS

This application is a continuation-in-part of application S.N. 10/743,451, filed on December 19, 2003, which is a continuation of application S.N. 10/603,006, filed on June 23, 2003, which is a continuation-in-part of application S.N. 10/348,231, filed January 21, 2003.

FIELD OF THE INVENTION

This invention relates to the isolation and production of cancerous disease modifying antibodies (CDMAB) and to the use of these CDMAB in therapeutic and diagnostic processes, optionally in combination with one or more chemotherapeutic agents. The invention further relates to binding assays which utilize the CDMAB of the instant invention.

BACKGROUND OF THE INVENTION

Each individual who presents with cancer is unique and has a cancer that is as different from other cancers as that person's identity. Despite this, current therapy treats all patients with the same type of cancer, at the same stage, in the same way. At least 30 percent of these patients will fail the first line of therapy, thus leading to further rounds of treatment and the increased probability of treatment failure, metastases, and ultimately, death. A superior

approach to treatment would be the customization of therapy for the particular individual. The only current therapy that lends itself to customization is surgery. Chemotherapy and radiation treatment cannot be tailored to the patient, and surgery by itself, in most cases is inadequate for producing cures.

With the advent of monoclonal antibodies, the possibility of developing methods for customized therapy became more realistic since each antibody can be directed to a single epitope. Furthermore, it is possible to produce a combination of antibodies that are directed to the constellation of epitopes that uniquely define a particular individual's tumor.

Having recognized that a significant difference between cancerous and normal cells is that cancerous cells contain antigens that are specific to transformed cells, the scientific community has long held that monoclonal antibodies can be designed to specifically target transformed cells by binding specifically to these cancer antigens; thus giving rise to the belief that monoclonal antibodies can serve as "Magic Bullets" to eliminate cancer cells.

Monoclonal antibodies isolated in accordance with the teachings of the instantly disclosed invention have been shown to modify the cancerous disease process in a manner which is beneficial to the patient, for example by reducing the tumor burden, and will variously be referred to herein as cancerous disease modifying antibodies (CDMAB) or "anti-cancer" antibodies.

At the present time, the cancer patient usually has few options of treatment. The regimented approach to cancer therapy has produced improvements in global survival and

morbidity rates. However, to the particular individual, these improved statistics do not necessarily correlate with an improvement in their personal situation.

Thus, if a methodology was put forth which enabled the practitioner to treat each tumor independently of other patients in the same cohort, this would permit the unique approach of tailoring therapy to just that one person. Such a course of therapy would, ideally, increase the rate of cures, and produce better outcomes, thereby satisfying a long-felt need.

Historically, the use of polyclonal antibodies has been used with limited success in the treatment of human cancers. Lymphomas and leukemias have been treated with human plasma, but there were few prolonged remissions or responses. Furthermore, there was a lack of reproducibility and no additional benefit compared to chemotherapy. Solid tumors such as breast cancers, melanomas and renal cell carcinomas have also been treated with human blood, chimpanzee serum, human plasma and horse serum with correspondingly unpredictable and ineffective results.

There have been many clinical trials of monoclonal antibodies for solid tumors. In the 1980s there were at least 4 clinical trials for human breast cancer which produced only 1 responder from at least 47 patients using antibodies against specific antigens or based on tissue selectivity. It was not until 1998 that there was a successful clinical trial using a humanized anti-Her2 antibody in combination with cisplatin. In this trial 37 patients were accessed for responses of which about a quarter had a partial response rate and another half had minor or stable disease progression.

The clinical trials investigating colorectal cancer involve antibodies against both

glycoprotein and glycolipid targets. Antibodies such as 17-1A, which has some specificity for adenocarcinomas, had undergone Phase 2 clinical trials in over 60 patients with only 1 patient having a partial response. In other trials, use of 17-1A produced only 1 complete response and 2 minor responses among 52 patients in protocols using additional cyclophosphamide. Other trials involving 17-1A yielded results that were similar. The use of a humanized murine monoclonal antibody initially approved for imaging also did not produce tumor regression. To date there has not been an antibody that has been effective for colorectal cancer. Likewise there have been equally poor results for lung, brain, ovarian, pancreatic, prostate, and stomach cancers. There has been some limited success in the use of an anti-GD3 monoclonal antibody for melanoma. Thus, it can be seen that despite successful small animal studies that are a prerequisite for human clinical trials, the antibodies that have been tested thus far, have been for the most part, ineffective.

PRIOR PATENTS

U.S. Patent No. 5,750,102 discloses a process wherein cells from a patient's tumor are transfected with MHC genes which may be cloned from cells or tissue from the patient. These transfected cells are then used to vaccinate the patient.

U.S. Patent No. 4,861,581 discloses a process comprising the steps of obtaining monoclonal antibodies that are specific to an internal cellular component of neoplastic and normal cells of the mammal but not to external components, labeling the monoclonal antibody, contacting the labeled antibody with tissue of a mammal that has received therapy to kill

neoplastic cells, and determining the effectiveness of therapy by measuring the binding of the labeled antibody to the internal cellular component of the degenerating neoplastic cells. In preparing antibodies directed to human intracellular antigens, the patentee recognizes that malignant cells represent a convenient source of such antigens.

U.S. Patent No. 5,171,665 provides a novel antibody and method for its production. Specifically, the patent teaches formation of a monoclonal antibody which has the property of binding strongly to a protein antigen associated with human tumors, e.g. those of the colon and lung, while binding to normal cells to a much lesser degree.

U.S. Patent No. 5,484,596 provides a method of cancer therapy comprising surgically removing tumor tissue from a human cancer patient, treating the tumor tissue to obtain tumor cells, irradiating the tumor cells to be viable but non-tumorigenic, and using these cells to prepare a vaccine for the patient capable of inhibiting recurrence of the primary tumor while simultaneously inhibiting metastases. The patent teaches the development of monoclonal antibodies which are reactive with surface antigens of tumor cells. As set forth at col. 4, lines 45 et seq., the patentees utilize autochthonous tumor cells in the development of monoclonal antibodies expressing active specific immunotherapy in human neoplasia.

U.S. Patent No. 5,693,763 teaches a glycoprotein antigen characteristic of human carcinomas is not dependent upon the epithelial tissue of origin.

U.S. Patent No. 5,783,186 is drawn to anti-Her2 antibodies which induce apoptosis in Her2 expressing cells, hybridoma cell lines producing the antibodies, methods of treating cancer using the antibodies and pharmaceutical compositions including said antibodies.

U.S. Patent No. 5,849,876 describes new hybridoma cell lines for the production of monoclonal antibodies to mucin antigens purified from tumor and non-tumor tissue sources.

U.S. Patent No. 5,869,268 is drawn to a method for generating a human lymphocyte producing an antibody specific to a desired antigen, a method for producing a monoclonal antibody, as well as monoclonal antibodies produced by the method. The patent is particularly drawn to the production of an anti-HD human monoclonal antibody useful for the diagnosis and treatment of cancers.

U.S. Patent No. 5,869,045 relates to antibodies, antibody fragments, antibody conjugates and single chain immunotoxins reactive with human carcinoma cells. The mechanism by which these antibodies function is two-fold, in that the molecules are reactive with cell membrane antigens present on the surface of human carcinomas, and further in that the antibodies have the ability to internalize within the carcinoma cells, subsequent to binding, making them especially useful for forming antibody-drug and antibody-toxin conjugates. In their unmodified form the antibodies also manifest cytotoxic properties at specific concentrations.

U.S. Patent No. 5,780,033 discloses the use of autoantibodies for tumor therapy and prophylaxis. However, this antibody is an anti-nuclear autoantibody from an aged mammal. In this case, the autoantibody is said to be one type of natural antibody found in the immune system. Because the autoantibody comes from "an aged mammal", there is no requirement that the autoantibody actually comes from the patient being treated. In addition the patent discloses natural and monoclonal anti-nuclear autoantibody from an aged mammal, and a hybridoma cell

line producing a monoclonal anti-nuclear autoantibody.

SUMMARY OF THE INVENTION

The instant inventors have previously been awarded U.S. Patent 6,180,357, entitled "Individualized Patient Specific Anti-Cancer Antibodies" directed to a process for selecting individually customized anti-cancer antibodies which are useful in treating a cancerous disease. For the purpose of this document, the terms "antibody" and "monoclonal antibody" (mAb) may be used interchangeably and refer to intact immunoglobulins produced by hybridomas (e.g. murine or human), immunoconjugates and, as appropriate, immunoglobulin fragments and recombinant proteins derived from immunoglobulins, such as chimeric and humanized immunoglobulins, F(ab') and $F(ab')_2$ fragments, single-chain antibodies, recombinant immunoglobulin variable regions (Fv)s, fusion proteins etc. It is well recognized in the art that some amino acid sequence can be varied in a polypeptide without significant effect on the structure or function of the protein. In the molecular rearrangement of antibodies, modifications in the nucleic or amino acid sequence of the backbone region can generally be tolerated. These include, but are not limited to, substitutions (preferred are conservative substitutions), deletions or additions. Furthermore, it is within the purview of this invention to conjugate standard chemotherapeutic modalities, e.g. radionuclides, with the CDMAB of the instant invention, thereby focusing the use of said chemotherapeutics. The CDMAB can also be conjugated to toxins, cytotoxic moieties, enzymes e.g. biotin conjugated enzymes, or hematogenous cells.

The prospect of individualized anti-cancer treatment will bring about a change in the way a patient is managed. A likely clinical scenario is that a tumor sample is obtained at the time of presentation, and banked. From this sample, the tumor can be typed from a panel of pre-existing cancerous disease modifying antibodies. The patient will be conventionally staged but the available antibodies can be of use in further staging the patient. The patient can be treated immediately with the existing antibodies and/or a panel of antibodies specific to the tumor can be produced either using the methods outlined herein or through the use of phage display libraries in conjunction with the screening methods herein disclosed. All the antibodies generated will be added to the library of anti-cancer antibodies since there is a possibility that other tumors can bear some of the same epitopes as the one that is being treated. The antibodies produced according to this method may be useful to treat cancerous disease in any number of patients who have cancers that bind to these antibodies.

Using substantially the process of US 6,180,370, the mouse monoclonal antibody 11BD-2E11-2 was obtained following immunization of mice with cells from a patient's breast tumor biopsy. Within the context of this application, anti-cancer antibodies having either cell-killing (cytotoxic) or cell-growth inhibiting (cytostatic) properties will hereafter be referred to as cytotoxic. This antibody can be used in aid of staging and diagnosis of a cancer, and can be used to treat tumor metastases. The 11BD-2E11-2 antigen was expressed on the cell surface of a broad range of human cell lines from different tissue origins. The breast cancer cell line MCF-7 and ovarian cancer cell line OVCAR-3 were the only two cancer cell lines tested that were susceptible to the cytotoxic effects of 11BD-2E11-2 as described in S/N 10/348,231.

The *in vitro* effects of 11BD-2E11-2 against breast and ovarian cancer cells were extended by establishing its anti-tumor activity *in vivo*. *In vivo* models of human cancer were established by implanting the MCF-7 breast cancer cells or OVCAR-3 ovarian cancer cells into severe combined immunodeficient (SCID) mice, as they are incapable of rejecting the human tumor cells due to a lack of certain immune cells. The effects of drugs tested in these kinds of pre-clinical xenograft tumor models are considered valid predictors of therapeutic efficacy. Cancer xenografts in mice grow as solid tumors developing parenchyma, stroma, central necrosis and neo-vasculature in the same manner as naturally occurring cancers. The mammary cancer cell line MCF-7 and the ovarian cancer cell line OVCAR-3 have been evaluated in SCID mice. The successful engraftment of both the MCF-7 and OVCAR-3 tumors and the sensitivity of the tumors to standard chemotherapeutic agents have characterized them as suitable models of human cancer for drug testing. The MCF-7 parental cell line and its variants and the OVCAR-3 cell line have been used successfully in xenograft tumor models to evaluate a wide range of therapeutic agents that have been used as clinical chemotherapeutic agents.

11BD-2E11-2 prevented tumor growth and reduced tumor burden in a preventative *in vivo* model of human breast cancer. Monitoring continued past 280 days post-treatment. 40 percent of the 11BD-2E11-2 treatment group was still alive at over 7.5 months post-implantation. Conversely, the isotype control group had 100 percent mortality after 6.5 months post-treatment. At day 51 (soon after last treatment), the mean tumor volume in the 11BD-2E11-2 treated group was 20% of the isotype control ($p=0.0098$). Therefore 11BD-2E11-2 enhanced and decreased the tumor burden compared to the control-treated groups in a

well-established model of human breast cancer.

In addition to the beneficial effects in a model of human breast cancer, 11BD-2E11-2 treatment also had anti-tumor activity against OVCAR-3 cells in an ovarian cancer model. Body weight was used a surrogate measure of tumor progression in this model. At day 80 post-implantation (16 days after the end of treatment) the mice in the treated group had 87.6 percent the mean body weight of the control group ($p=0.015$). Thus, 11BD-2E11-2 treatment was efficacious as it delayed tumor progression compared to the buffer control treated group in a well-established model of human ovarian cancer. The anti-tumor activities of 11BD-2E11-2, in several different cancer models, make it an attractive anti-cancer therapeutic agent.

In all, this invention teaches the use of the 11BD-2E11-2 antigen as a target for a therapeutic agent, that when administered can reduce the tumor burden of a cancer expressing the antigen in a mammal, and can also lead to a prolonged survival of the treated mammal. This invention also teaches the use of CDMAB (11BD-2E11-2), and its derivatives, to target its antigen to reduce the tumor burden of a cancer expressing the antigen in a mammal, and to prolong the survival of a mammal bearing tumors that express this antigen.

If a patient is refractory to the initial course of therapy or metastases develop, the process of generating specific antibodies to the tumor can be repeated for re-treatment. Furthermore, the anti-cancer antibodies can be conjugated to red blood cells obtained from that patient and re-infused for treatment of metastases. There have been few effective treatments for metastatic cancer and metastases usually portend a poor outcome resulting in death. However, metastatic cancers are usually well vascularized and the delivery of anti-cancer antibodies by red blood cells can have the effect of concentrating the antibodies at the site of

the tumor. Even prior to metastases, most cancer cells are dependent on the host's blood supply for their survival and an anti-cancer antibody conjugated to red blood cells can be effective against *in situ* tumors as well. Alternatively, the antibodies may be conjugated to other hematogenous cells, e.g. lymphocytes, macrophages, monocytes, natural killer cells, etc.

There are five classes of antibodies and each is associated with a function that is conferred by its heavy chain. It is generally thought that cancer cell killing by naked antibodies are mediated either through antibody-dependent cell-mediated cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDC). For example murine IgM and IgG2a antibodies can activate human complement by binding the C-1 component of the complement system thereby activating the classical pathway of complement activation which can lead to tumor lysis. For human antibodies, the most effective complement activating antibodies are generally IgM and IgG1. Murine antibodies of the IgG2a and IgG3 isotype are effective at recruiting cytotoxic cells that have Fc receptors which will lead to cell killing by monocytes, macrophages, granulocytes and certain lymphocytes. Human antibodies of both the IgG1 and IgG3 isotype mediate ADCC.

Another possible mechanism of antibody mediated cancer killing may be through the use of antibodies that function to catalyze the hydrolysis of various chemical bonds in the cell membrane and its associated glycoproteins or glycolipids, so-called catalytic antibodies.

There are two additional mechanisms of antibody mediated cancer cell killing which are more widely accepted. The first is the use of antibodies as a vaccine to induce the body to produce an immune response against the putative antigen that resides on the cancer cell. The

second is the use of antibodies to target growth receptors and interfere with their function or to down regulate that receptor so that effectively its function is lost.

The clinical utility of a cancer drug is based on the benefit of the drug under an acceptable risk profile to the patient. In cancer therapy survival has generally been the most sought after benefit, however there are a number of other well-recognized benefits in addition to prolonging life. These other benefits, where treatment does not adversely affect survival, include symptom palliation, protection against adverse events, prolongation in time to recurrence or disease-free survival, and prolongation in time to progression. These criteria are generally accepted and regulatory bodies such as the U.S. Food and Drug Administration (F.D.A.) approve drugs that produce these benefits (Hirschfeld et al. Critical Reviews in Oncology/Hematolgy 42:137-143 2002). In addition to these criteria it is well-recognized that there are other endpoints that may presage these types of benefits. In part, the accelerated approval process granted by the U.S. F.D.A. acknowledges that there are surrogates that will likely predict patient benefit. As of year-end (2003), there has been sixteen drugs approved under this process, and of these, four have gone on to full approval, i.e., follow-up studies have demonstrated direct patient benefit as predicted by surrogate endpoints. One important endpoint for determining drug effects in solid tumors is the assessment of tumor burden by measuring response to treatment (Therasse et al. Journal of the National Cancer Institute 92(3):205-216 2000). The clinical criteria (RECIST criteria) for such evaluation have been promulgated by Response Evaluation Criteria in Solid Tumors Working Group, a group of international experts in cancer. Drugs with a demonstrated effect on tumor burden, as shown by objective responses according to RECIST criteria, in comparison to the appropriate control

group tend to, ultimately, produce direct patient benefit. In the pre-clinical setting tumor burden is generally more straightforward to assess and document. In that pre-clinical studies can be translated to the clinical setting, drugs that produce prolonged survival in pre-clinical models have the greatest anticipated clinical utility. Analogous to producing positive responses to clinical treatment, drugs that reduce tumor burden in the pre-clinical setting may also have significant direct impact on the disease. Although prolongation of survival is the most sought after clinical outcome from cancer drug treatment, there are other benefits that have clinical utility and it is clear that tumor burden reduction can also lead to direct benefits and have clinical impact (Eckhardt et al. Developmental Therapeutics: Successes and Failures of Clinical Trial Designs of Targeted Compounds; ASCO Educational Book, 39th Annual Meeting, 2003, pages 209-219).

Accordingly, it is an objective of the invention to utilize a method for producing CDMAB from cells derived from a particular individual which are cytotoxic with respect to cancer cells while simultaneously being relatively non-toxic to non-cancerous cells, in order to isolate hybridoma cell lines and the corresponding isolated monoclonal antibodies and antigen binding fragments thereof for which said hybridoma cell lines are encoded.

It is an additional objective of the invention to teach CDMAB and antigen binding fragments thereof.

It is a further objective of the instant invention to produce CDMAB whose cytotoxicity is mediated through ADCC.

It is yet an additional objective of the instant invention to produce CDMAB whose

cytotoxicity is mediated through CDC.

It is still a further objective of the instant invention to produce CDMAB whose cytotoxicity is a function of their ability to catalyze hydrolysis of cellular chemical bonds.

A still further objective of the instant invention is to produce CDMAB which are useful in a binding assay for the diagnosis, prognosis, and monitoring of cancer.

Other objects and advantages of this invention will become apparent from the following description wherein are set forth, by way of illustration and example, certain embodiments of this invention.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1. Effect of 11BD-2E11-2 on tumor growth in a preventative MCF-7 breast cancer model. The dashed line indicates the period during which the antibody was administered. Data points represent the mean +/- SEM.

Figure 2. Survival of tumor-bearing mice after treatment with 11BD-2E11-2 or isotype control antibody in a preventative MCF-7 xenograft study. Mice were monitored for survival for longer than 230 days post-treatment.

Figure 3. Effect of 11BD-2E11-2 on mean body weight in a preventative OVCAR-3 ovarian cancer model. The solid line indicates the period during which the antibody was administered. Data points represent the mean +/- SEM.

Figure 4. Survival of tumor-bearing mice after treatment with 11BD-2E11-2 or buffer control antibody in a preventative OVCAR-3 study. Mice were monitored for survival for

approximately 60 days post-treatment.

DETAILED DESCRIPTION OF THE INVENTION

EXAMPLE 1

The hybridoma cell line 11BD-2E11-2 was deposited, in accordance with the Budapest Treaty, with the American Type Culture Collection, 10801 University Blvd., Manassas, VA 20110-2209 on November 11th, 2003, under Accession Number PTA-5643. In accordance with 37 CFR 1.808, the depositors assure that all restrictions imposed on the availability to the public of the deposited materials will be irrevocably removed upon the granting of a patent.

11BD-2E11-2 monoclonal antibody was produced by culturing the hybridomas in CL-1000 flasks (BD Biosciences, Oakville, ON) with collections and reseeding occurring twice/week and with purification according to standard antibody purification procedures with Protein G Sepharose 4 Fast Flow (Amersham Biosciences, Baie d'Urfé, QC).

In Vivo MCF-7 Preventative Survival Tumor Experiment

With reference to Figures 1 and 2, 4 to 8 week old female SCID mice were implanted with 5 million MCF-7 human breast cancer cells in 100 microlitres saline injected subcutaneously in the scruff of the neck. The mice were randomly divided into 2 treatment groups of 11-13 mice. On the day after implantation, 20 mg/kg of either 11BD-2E11-2 test antibody or isotype control antibody (known not to bind MCF-7 or OVCAR-3 cells) was administered intraperitoneally at a volume of 300 microliters after dilution from the stock

concentration with a diluent that contained 2.7 mM KCl, 1 mM KH_2PO_4, 137 mM NaCl and 20 mM Na_2HPO_4. The antibodies were then administered once per week for a period of 7 weeks in the same fashion. Tumor growth was measured about every seventh day with calipers for up to 8 weeks or until individual animals reached the Canadian Council for Animal Care (CCAC) end-points. Body weights of the animals were recorded for the duration of the study. At the end of the study all animals were euthanised according to CCAC guidelines.

11BD-2E11-2 significantly reduced the tumor burden in treated mice in comparison to controls (Figure 1). After treatment (day 51), 11BD-2E11-2 prevented tumor growth by 80 percent ($p=0.0098$) in comparison to isotype control antibody treated mice. There was also a post-treatment survival benefit (Figure 2) associated with 11BD-2E11-2 administration. The isotype control antibody treated group reached 100 percent mortality by day 197 post-treatment while 40 percent of the 11BD-2E11-2 treated group were still alive at day 233. In summary, 11BD-2E11-2 increased survival and decreased tumor burden in a well-established model of human breast cancer (Blakey et al. Clinical Cancer Research 8:1974-1983 2002; Klement et al. Clinical Cancer Research 8:221-232 2002; Waud et al. Relevance of Tumor Models for Anticancer Drug Development, Fiebig and Burger, eds. 54:305-315 1999; Karpanen et al. Cancer Research 61:1786-1790 2001).

EXAMPLE 2

In Vivo OVCAR-3 Preventative Tumor Experiments

With reference to the data shown in Figures 3 and 4, 4 to 8 week old, female SCID mice were implanted with 5 million OVCAR-3 human ovarian cancer cells in 1000 microliters

saline injected intraperitoneally. The mice were randomly divided into 2 treatment groups of 10. On the day after implantation, 20 mg/kg of 11BD-2E11-2 test antibody or buffer control antibody was administered intraperitoneally at a volume of 300 microliters after dilution from the stock concentration with a diluent that contained 2.7 mM KCl, 1 mM KH_2PO_4, 137 mM NaCl and 20 mM Na_2HPO_4. The antibodies were then administered once per week for a period of 9 weeks in the same fashion. Body weights of the animals were recorded for the duration of the study. At the end of the study all animals were euthanised according to CCAC guidelines.

In the OVCAR-3 ovarian cancer xenograft model, increasing body weight can be used as a surrogate indicator of disease progression since this reflects the accumulation of ascites from increased tumor burden (Figure 3). At day 80 post-implantation (16 days after the end of treatment), 11BD-2E11-2 administration prevented body weight gain by 12.4 percent ($p=0.015$) compared to the buffer control group. Mice were monitored post-treatment for survival (Figure 4). By day 87, the buffer control group had reached 90 percent mortality while the 11BD-2E11-2 treated group still had 80 percent survival. The 11BD-2E11-2 treated group did not reach 90 percent mortality until day 125. In summary, 11BD-2E11-2 antibody treatment reduced tumor burden, delayed disease progression and enhanced survival in comparison to a buffer control antibody in a well-recognized model of human ovarian cancer. Therefore treatment with 11BD-2E11-2 significantly decreased the tumor burden of established tumors in two well-recognized models of human cancer disease (breast and ovarian cancers) suggesting pharmacologic and pharmaceutical benefits of this antibody for therapy in other mammals, including man (Smith et al. The Prostate 48:47-53 2001; Olson et al. International Journal of Cancer 98:923-929 2002; Guilbaud et al. Clinical Cancer Research

7:2573-2580 2001; Von Gruenigen et al. International Journal of Gynecologic Cancer 9:365-372 1999; Guichard et al. Clinical Cancer Research 7:3222-3228 2001; Xiao et al. Protein Expression and Purification 19:12-21 2000).

All patents and publications mentioned in this specification are indicative of the levels of those skilled in the art to which the invention pertains. All patents and publications are herein incorporated by reference to the same extent as if each individual publication was specifically and individually indicated to be incorporated by reference.

It is to be understood that while a certain form of the invention is illustrated, it is not to be limited to the specific form or arrangement of parts herein described and shown. It will be apparent to those skilled in the art that various changes may be made without departing from the scope of the invention and the invention is not to be considered limited to what is shown and described in the specification. One skilled in the art will readily appreciate that the present invention is well adapted to carry out the objects and obtain the ends and advantages mentioned, as well as those inherent therein. Any oligonucleotides, peptides, polypeptides, biologically related compounds, methods, procedures and techniques described herein are presently representative of the preferred embodiments, are intended to be exemplary and are not intended as limitations on the scope. Changes therein and other uses will occur to those skilled in the art which are encompassed within the spirit of the invention and are defined by the scope of the appended claims. Although the invention has been described in connection with specific preferred embodiments, it should be understood that the invention as claimed should not be unduly limited to such specific embodiments. Indeed, various modifications of the described modes for carrying out the invention which are obvious to those skilled in the art

are intended to be within the scope of the following claims.